EXTENDED REPORT

Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis

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Objectives: To evaluate the effect of infliximab on health related quality of life (HRQoL) and physical function in patients with active psoriatic arthritis (PsA) in the IMPACT 2 trial.

Methods: 200 patients with PsA unresponsive to conventional treatment were randomised to intravenous infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, 6, 14, and 22; patients with inadequate response entered early escape at week 16. HRQoL was assessed using the Short Form-36 (SF-36) at weeks 0, 14, and 24. Functional disability was assessed using the Health Assessment Questionnaire (HAQ) at every visit through week 24. Associations between changes in quality of life (SF-36) and articular (American College of Rheumatology (ACR)) and dermatological (Psoriasis Area and Severity Index (PASI)) responses were examined.

Results: Mean percentage improvement from baseline in HAQ was 48.6% in the infliximab group compared with worsening of 18.4% in the placebo group at week 14 ($p<0.001$). Furthermore, 58.6% and 19.4% of infliximab and placebo treated patients, respectively, achieved a clinically meaningful improvement in HAQ (that is, ≥ 0.3 unit decrease) at week 14 ($p<0.001$). Increases in physical and mental component summary (PCS and MCS) scores and all eight scales of the SF-36 in the infliximab group were greater than those in the placebo group at week 14 ($p \leq 0.001$). These benefits were sustained through week 24. Patients achieving ACR20 and PASI75 responses had the greatest improvements in PCS and MCS scores.

Conclusions: In patients with PsA, infliximab 5 mg/kg significantly improved HRQoL and physical function compared with placebo through 24 weeks.

Psoriatic arthritis (PsA), a chronic and inflammatory arthritis associated with psoriatic skin lesions, can significantly affect quality of life. The majority of patients with PsA develop erosive arthropathy,[1–3] and the radiological severity in the hands and feet is comparable between patients with rheumatoid arthritis (RA) and those with PsA.[4] Despite the fact that patients with RA may have more peripheral joint damage than those with PsA, the added burden of skin disease in patients with PsA can reduce physical function and quality of life to a similar extent among patients with these diseases.[5] Although patients with PsA reportedly had higher levels of vitality as measured by the Short Form-36 (SF-36) in a comparative study of PsA and RA, they also reported more role limitations due to emotional problems and more bodily pain.[6] Again, the extent of disability among patients with PsA may be attributed to the fact that these patients have an inflammatory skin condition as well as peripheral joint disease. The psychological and social effects of skin involvement have been well documented in patients with psoriasis.[7–11] Indeed, when compared with patients with other diseases, such as cancer, arthritis, hypertension, heart disease, diabetes, and depression, patients with psoriasis reported a similar reduction in health related quality of life (HRQoL).[12]

Tumour necrosis factor alpha (TNFα), one of several proinflammatory cytokines thought to have an important role in the potentiation of inflammatory responses, has been found to be increased in the skin and synovium of patients with PsA.[13–15] Emerging evidence indicates that TNF blockade with etanercept[16 17] and infliximab[18 19] is especially effective in reducing the clinical signs and symptoms of joint disease and improving the skin component as well as the quality of life in patients with this frequently disabling condition.[20 21]

The IMPACT 2 trial was a phase III, multicentre, double blind, placebo controlled study conducted to evaluate the efficacy and safety of infliximab in patients with PsA. In that study a significantly greater proportion of infliximab treated patients than placebo treated patients achieved significant improvement in the articular as well as the dermatological manifestations of the disease. The purpose of this report is to examine in greater detail the effect of infliximab treatment on HRQoL and physical function. Understanding the impact of treatments on these measures in patients with PsA is important because improving patient wellbeing is a key therapeutic objective. The final objective is to examine the relative importance of skin and joint responses for improving HRQoL.

PATIENTS AND METHODS

Study design

The details of the study design and eligibility criteria have been described elsewhere.[19] IMPACT 2 was a phase III, multicentre, parallel group study, in which eligible patients had to have active PsA diagnosed at least 6 months before starting the study treatment and previous treatment with disease modifying antirheumatic drugs or non-steroidal anti-inflammatory drugs had to have failed. Patients were also required to have active psoriasis, with at least one qualifying target lesion ≥ 2 cm in diameter.

Abbreviations: ACR, American College of Rheumatology; HAQ, Health Assessment Questionnaire; HRQoL, health related quality of life; MCS, mental component summary; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFα, tumour necrosis factor α

Two hundred patients were randomised in a 1:1 ratio to receive intravenous infusions of either placebo or infliximab 5 mg/kg at weeks 0, 2, and 6, followed by maintenance dosing at weeks 14 and 22. Randomisation was stratified by investigational site and current methotrexate (MTX) use. At week 16, patients in both treatment groups who had less than 10% improvement from baseline in both swollen and tender joint counts were eligible to enter early escape, which allowed patients in the placebo group with active disease to remain in the trial and receive infliximab 5 mg/kg treatment before week 24. To maintain the blind, patients in the infliximab group who entered early escape received placebo infusions at weeks 16 and 18 and another infliximab 5 mg/kg infusion at week 22.

Patient evaluations

The Disability Index of the Health Assessment Questionnaire (HAQ) was used to assess the functional status of patients at all study visits (weeks 0, 2, 6, 14, 22, and 24). This is a 20 question instrument that evaluates the degree of difficulty a person has in accomplishing tasks in eight functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area.[22] A clinically meaningful change in HAQ is the level at which patients can reliably detect improvement in function; for patients with PsA, the clinically meaningful change in HAQ has been reported to be 0.3.[23]

To evaluate quality of life, the SF-36 was administered to patients at weeks 0, 14, and 24. The SF-36 consists of 36 items that are aggregated into eight multi-item scales: physical functioning (limitations in performing physical activities), role-physical (problems with work or daily activities due to physical health), bodily pain (magnitude of pain and limitations due to pain), general health, vitality (tiredness or lack of energy), social functioning (interference with social activities due to physical or emotional problems), role-emotional (problems with work or daily activities due to emotional factors), and mental health (nervousness and depression).[24] This instrument has been extensively validated for use in multiple disease states as well as in diverse healthy populations. Two summary measures of the SF-36 (that is, the physical component summary (PCS) and the mental component summary (MCS) scores) are derived by aggregating the eight scales as factor components. Changes of 3 or more in the MCS, PCS, and norm based SF-36 scale scores were considered clinically meaningful in patients with RA.[25] The average threshold for clinically meaningful change in the raw SF-36 scale scores was found to range from 2.4 for general health to 16.4 for role-emotional.[26] Articular responses were assessed using the American College of Rheumatology (ACR) response criteria.[27]

Dermatological responses were assessed using the Psoriasis Area and Severity Index (PASI) scores, and improvements of at least 50% and 75% in the PASI (PASI50 and PASI75) were calculated. The PASI is a composite score (range 0–72) used to evaluate the severity of psoriatic lesions by assessing the extent of skin involvement, erythema, plaque thickness, and degree of scaling.[28] Articular and dermatological responses of patients in this study have been reported elsewhere.[19]

Statistical methods

Each of the eight SF-36 scale scores was calculated using both the standard method and the norm based methods that standardise the scores such that the mean (SD) for the general American population is 50 (10).[29] Analysis of variance on van der Waerden scores was used to compare the percentage change from baseline for the HAQ and the change from baseline for the SF-36 between the two treatment groups. A χ^2 test was used to compare the proportion of patients who achieved a clinically meaningful improvement in HAQ (defined as at least a 0.3 unit decrease) between treatment groups. Changes in the SF-36 scores, including the MCS and PCS scores as well as the individual scales, were calculated by the ACR and PASI response or non-response. In all analyses, if a patient entered early escape at week 16, the values of the last observation before the week 16 visit were carried forward to week 24.

Table 1 Baseline characteristics of patients

Characteristics	Placebo	Infliximab 5 mg/kg
Demographics		
Age (years), mean (SD)	46.5 (11.3)	47.1 (12.8)
Sex, male (%)	51 (51)	71 (71)
Race, white (%)	94 (94)	95 (95)
*Baseline disease characteristics**		
PsA duration (years)	7.5	8.4
Psoriasis duration (years)	16.8	16.2
Patients with at least 3% BSA psoriasis involvement (%)	87/98 (89)	83/100 (83)
PASI score (0–72)	10.2	11.4
Number of swollen joints (0–66)	14.4	13.9
Number of tender joints (0–68)	25.1	24.6
Duration of morning stiffness (0–1440 min)	183.4	216.0
Patient's assessment of pain (VAS; 0–10 cm)	5.9	5.6
*Physical function/quality of life**		
HAQ score (0–3)	1.1	1.1
PCS score of SF-36	31.0	33.0
MCS score of SF-36	47.0	45.5

*Unless otherwise specified, data are expressed as means.
PsA, psoriatic arthritis; BSA, body surface area; PASI, Psoriasis Area and Severity Index; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; PCS, physical component summary; MCS, mental component summary; SF-36, Short Form-36.

RESULTS

Patient characteristics

The patient demographics and baseline disease characteristics were comparable between the two treatment groups, with the exception of the higher proportion of men (71%) in the infliximab group than in the placebo group (51%). An overall summary of the key disease characteristics across the two groups indicates that the patients enrolled in this trial had active disease (table 1). At baseline, similar proportions of patients in each treatment group were receiving MTX: 45% in the placebo group and 47% in the infliximab group. There was no substantial difference in baseline disease activity between patients who were receiving MTX and those who were not.

The SF-36 scores were similar between the two treatment groups at baseline (table 1). The mean PCS and MCS scores at baseline were lower than those of the general American population (50 (10)). Figure 1 illustrates the difference between the PCS and MCS score distributions of the IMPACT 2 patients at baseline and those of the general American population. The baseline mean HAQ score was 1.1, which is consistent with moderate disability and impaired physical function.

Health Assessment Questionnaire

At both weeks 14 and 24, the HAQ score for patients in the infliximab group had improved significantly compared with

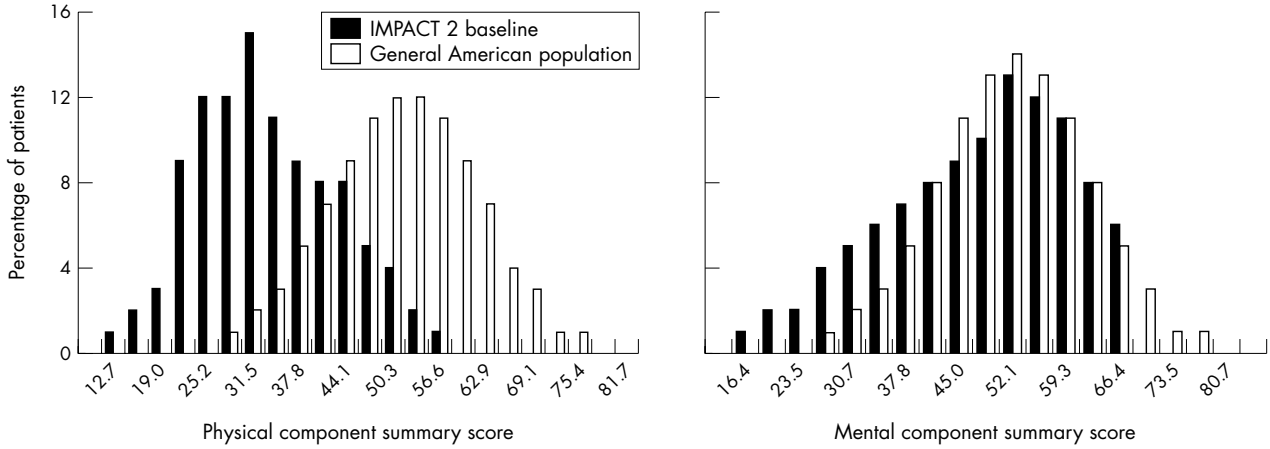

Figure 1 Distribution of PCS and MCS scores of the SF-36 for patients in the IMPACT 2 study at baseline (n = 199) and an American general population group (n = 2474). SF-36, Short Form-36.

that for the placebo patients. Figure 2 shows that significant improvements in HAQ scores in the infliximab group compared with the placebo group were evident as early as week 2, and this trend was maintained through the 24 week study period. The mean HAQ scores remained unchanged from baseline at both weeks 14 and 24 in the placebo group but decreased to 0.7 at both time points in the infliximab group. The mean percentage improvement in HAQ was 48.6% in the infliximab group compared with –18.4% (worsening) in the placebo group at week 14 ($p<0.001$); results were similar at week 24 (46.0% improvement versus –19.4% worsening; $p<0.001$). At week 14, 58.6% of patients in the infliximab group achieved a clinically meaningful improvement in HAQ (that is, at least a 0.3 decrease) compared with 19.4% in the placebo group ($p<0.001$); this benefit was maintained at week 24 (52.1% versus 20.0%; $p<0.001$).

Significant improvement in HAQ scores was seen in the infliximab group compared with the placebo group, regardless of MTX use at baseline. For patients who were receiving MTX at baseline, the mean percentage improvement in HAQ at week 14 was 34.1% in the infliximab group compared with 3.7% in the placebo group ($p<0.01$). For patients who were not receiving MTX, the corresponding figures were 61.6% and –36.4% (worsening; $p<0.001$). A similar pattern was found for this analysis at week 24.

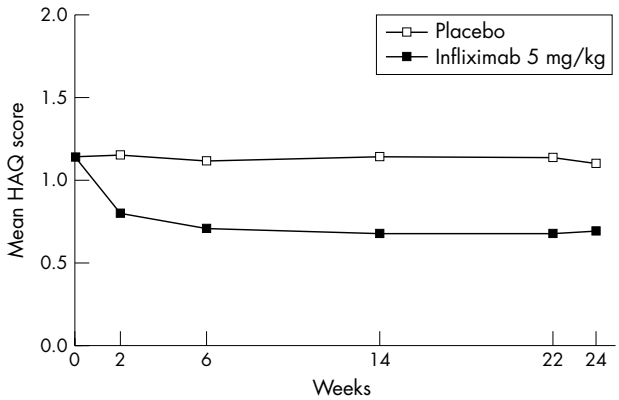

Figure 2 Physical function over time, as measured by mean HAQ scores in patients with PsA treated with infliximab or placebo; higher HAQ score indicates lower physical function (HAQ = Disability Index of the Health Assessment Questionnaire).

Short Form-36

The improvement in both the PCS and MCS scores and the raw scores for all eight scales of the SF-36 in the infliximab group was greater than that in the placebo group at both weeks 14 and 24 (table 2). At week 14, all between-group differences were highly significant ($p<0.01$); these differences also exceeded the threshold for a clinically meaningful difference.[26] At week 24, all differences were significant ($p<0.05$), with the exception of the role-emotional scale, which approached a significant level ($p = 0.093$). The mean improvement in the PCS score was 9.1 in the infliximab group compared with 1.1 in the placebo group at week 14; and 7.7 compared with 1.3 at week 24 ($p<0.001$ at both time points). The mean improvement in the MCS score was 3.8 in the infliximab group compared with −1.2 (worsening) in the placebo group at week 14 ($p = 0.001$); and 3.9 compared with 0.4 at week 24 ($p<0.05$).

Significant benefits, as measured by SF-36 scores, were seen in the infliximab group compared with the placebo group, regardless of baseline use of MTX. For patients who were receiving MTX at baseline, the mean improvement from baseline at week 14 was 7.9 in the infliximab group versus 2.9 in the placebo group ($p<0.01$) for the PCS score and 2.0 in the infliximab group versus –3.4 (worsening) in the placebo group ($p<0.05$) for the MCS score. For patients who were not receiving MTX at baseline, the corresponding improvement was 10.1 in the infliximab group versus –0.5 (worsening) in the placebo group ($p<0.001$) for the PCS score and 5.3 in the infliximab group versus 0.6 in the placebo group ($p<0.05$) for the MCS score. A similar pattern was found when the data were analysed at week 24.

Figure 3 shows the norm-based scores for the component summaries and the individual scales at baseline as well as the change from baseline to week 14. This figure demonstrates that the SF-36 scores in the infliximab group at week 14 improved towards a level consistent with the average level of the general American population. Notably, the mean MCS score in the infliximab group at week 14 was similar to that in the general American population. The mean percentage change from baseline to week 14 in PCS and MCS scores was 32.6% and 6.0%, respectively, in the infliximab group and 14.5% and –0.2%, respectively, in the placebo group.

Relationship of the SF-36 with ACR and PASI improvement

Figure 4 illustrates that greater improvements in PCS and MCS scores were associated with greater improvements in

Table 2 Change from baseline in Health Assessment Questionnaire and Short Form-36 scores

	Week 14			Week 24		
	Placebo	Infliximab	p Value	Placebo	Infliximab	p Value
HAQ						
Percentage improvement*	−18.4	48.6	<0.001	−19.4	46.0	<0.001
Percentage of patients with at least a 0.3 decrease	19.4	58.6	<0.001	20.0	52.1	<0.001
*SF-36**						
PCS	1.1	9.1	<0.001	1.3	7.7	<0.001
MCS	−1.2	3.8	0.001	0.4	3.9	0.047
PF	−0.2	17.7	<0.001	1.3	15.3	<0.001
RP	5.2	30.1	<0.001	9.4	25.5	0.010
BP	3.2	22.9	<0.001	4.0	21.6	<0.001
GH	−2.6	11.9	<0.001	−1.8	9.4	<0.001
VT	1.9	12.7	<0.001	1.5	12.8	<0.001
SF	−0.5	13.4	<0.001	2.6	12.9	0.007
RE	−4.9	16.8	0.002	1.4	13.3	0.093
MH	−1.6	9.1	<0.001	1.3	9.4	0.002

*Data are expressed as means, and p values were based on a non-parametric analysis.
HAQ, Health Assessment Questionnaire; SF-36, Short Form-36; PCS, physical component summary; MCS, mental component summary; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health.

ACR and PASI. Specifically, patients who had a PASI50 but not a PASI75 response had a smaller increase in SF-36 scores than patients who had a PASI75 response. Similarly, patients who achieved an ACR20 but not an ACR50 response had a smaller improvement in SF-36 scores than patients who achieved ACR50.

Table 3 shows the relative contribution of articular and dermatological responses to the various mental and physical aspects of quality of life in patients with PsA treated with infliximab. The data show that at week 14 patients who achieved both ACR20 and PASI75 responses had the greatest improvement in both the PCS (mean change 13.0) and the MCS (5.4) scores. Also, patients who achieved neither ACR20 nor PASI75 response had very little change in either the PCS (0.6) or the MCS (−1.0) scores. Interestingly, patients who achieved an ACR20 response but not a PASI75 response had greater improvement in the PCS scores (9.3) but slightly less improvement in the MCS scores (1.9) than those who achieved a PASI75 response but not an ACR20 response (where PCS and MCS score improvements were 5.7 and 3.5, respectively). This difference in the MCS score seemed to be driven by the role-emotional scale (table 3). This suggests that articular involvement may have a greater effect on the physical component of the quality of life in patients with PsA, whereas dermatological involvement may have a greater effect on the mental component.

DISCUSSION

Better understanding of HRQoL and physical function in PsA has underlined the impact of the disease on both the physical and mental wellbeing of patients. One of the primary goals of treatment of patients with PsA, therefore, is to enhance wellbeing by improving overall HRQoL and optimising functional status. Studies have shown that physical function

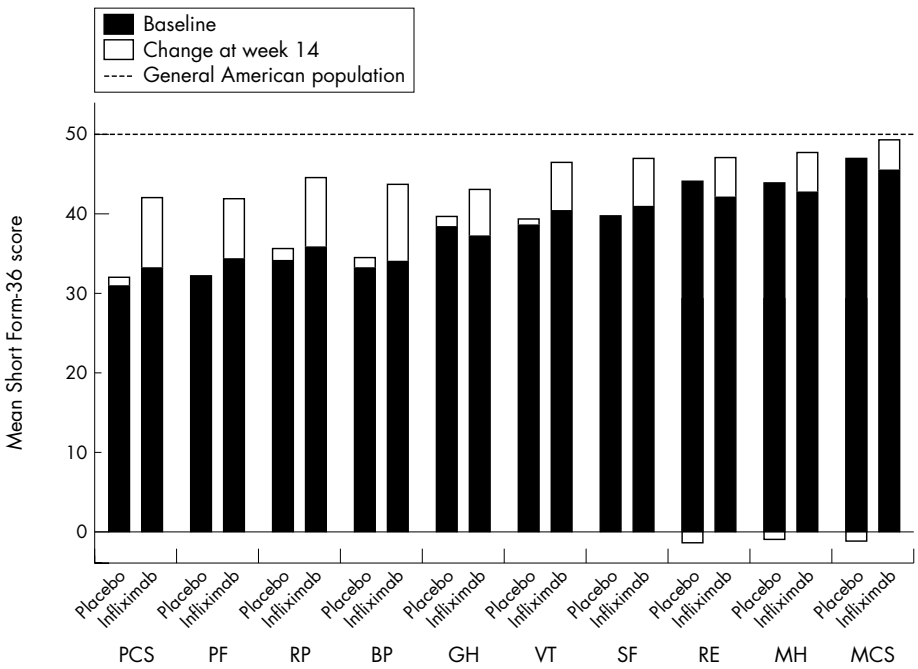

Figure 3 Mean scores for the PCS and MCS as well as the norm-based scores of the eight individual scales of the SF-36 at baseline and week 14 in the placebo and infliximab treatment groups. PCS, physical component summary; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; MCS, mental component summary; SF-36, Short Form-36.

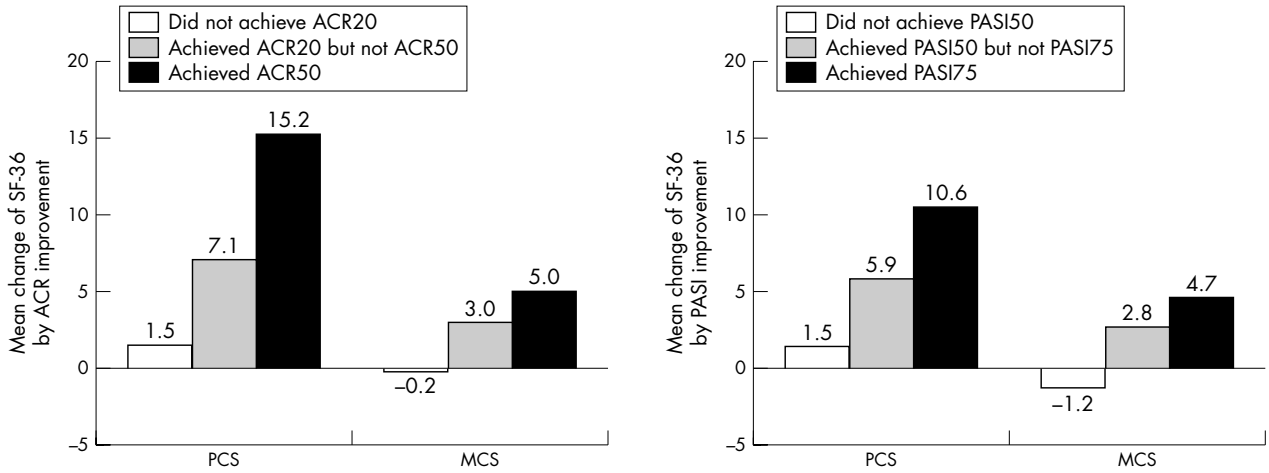

Figure 4 Relationships between improvements in PCS and MCS scores of the SF-36 and improvements in ACR and PASI from baseline to week 14. ACR20, at least 20% improvement according to ACR criteria; ACR50, at least 50% improvement according to ACR criteria; PASI50, at least 50% improvement from baseline in PASI score; PASI75, at least 75% improvement from baseline in PASI score; MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36.

and HRQoL scores in patients with PsA are similar to those in patients with RA .[5 6] Furthermore, besides the burden of joint disease, patients with PsA must cope with the unique challenges related to the dermatological aspects of the disease.[7–11] Functional status has important implications for work ability in patients with arthritis, which is especially relevant to the pharmacoeconomic considerations of treatment. Thus, treatments that substantially improve functional status may be cost effective, even if their acquisition costs are relatively high.[30]

In the IMPACT 2 study, SF-36 and HAQ scores were used to measure the effect of infliximab on HRQoL and physical function, respectively, in PsA. These two measures have been shown to be responsive to changes in health among patients with PsA.[31] Physical functioning change scores for HAQ and SF-36 over a 12–18 month period discriminated between patients who improved and those who did not improve over the same period.[32] The SF-36, which has been widely validated in the general population as well as in patients with various diseases, is a particularly useful instrument for comparing relative HRQoL, both physical and mental, among different diseases and between patient populations and the general public.[29] HAQ, which is relatively specific for the effect of arthritis on functional ability, has been correlated with disease activity in patients with PsA and is recommended as an accepted outcome measure of physical function in PsA clinical trials.[33] The number of actively inflamed joints and the number of damaged joints predict transition rates between physical disability states, based on the HAQ.[34]

Table 3 Mean improvement from baseline to week 14 in SF-36 scores by categories of ACR20 and PASI75 response or non-response

	ACR20 non-responders		ACR20 responders	
	PASI75 non-responders	PASI75 responders	PASI75 non-responders	PASI75 responders
PCS	0.6	5.7	9.3	13.0
MCS	−1.0	3.5	1.9	5.4
PF	−1.6	9.6	18.2	27.6
RP	3.6	28.3	30.0	38.6
BP	3.1	12.0	22.3	32.5
GH	−2.5	7.8	7.8	18.4
VT	0.6	9.6	13.8	18.3
SF	−1.0	9.2	11.5	19.9
RE	−3.6	17.4	6.7	22.7
MH	−1.7	6.3	7.5	13.3

ACR, American College of Rheumatology; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; MCS, mental component summary; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; SF-36, Short Form-36.

The baseline SF-36 scores among the patients enrolled in the IMPACT 2 study were lower than those in the general American population, indicating impaired HRQoL. The PCS and MCS scores at baseline showed that patients had a lower baseline level of HRQoL for both physical and psychosocial aspects than the general American population. Furthermore, the patients enrolled in the IMPACT 2 trial had an impaired HRQoL, as measured by the SF-36, to an extent comparable to that seen among patients with severe RA who were enrolled in infliximab trials.[35 36] Likewise, the baseline HAQ scores in each treatment group demonstrated that the patients had impaired physical function.

All SF-36 summary components and individual scales improved in patients treated with infliximab in this study. The increases in both the PCS and MCS scores and most of the individual scales of the SF-36 in the infliximab group were significantly greater than those in the placebo group both at weeks 14 and 24. The magnitude of improvement in both the PCS and MCS scores exceeded the threshold for clinically meaningful improvement used in other studies.[25] In fact, the magnitude of improvement seen with infliximab treatment in IMPACT 2 is comparable to the mean changes in PCS (9.6) and MCS (3.7) scores seen in patients after hip replacement.[29]

The improvements in the PCS and MCS scores were consistent among patients who were receiving MTX at baseline and those who were not. However, this might have been expected based upon the study design. Thus, by selecting patients based on measures of disease activity, irrespective of concomitant MTX use, the ability to detect potential additive effects was probably precluded. In RA, studies of treatment-naïve patients who were randomised to MTX, TNF inhibitor, or the combination showed that the combination approach resulted in better outcomes, particularly for radiographic changes.[37 38] Whether or not additive or

synergistic efficacy may be achieved by such a therapeutic approach in patients with PsA remains to be determined.

In this study the improvements in HAQ were significant in the infliximab treated patients compared with placebo treated patients, and the results were consistent among patients who were receiving MTX at baseline and those who were not. Response was rapid and significant, with patients, on average, achieving normal or near normal scores by the end of the study.[22] Whereas more than one half of the patients in the infliximab group achieved a clinically meaningful improvement in HAQ, less than one quarter of patients in the placebo group crossed that threshold. This improvement represents a significant benefit to the patients in their ability to undertake daily activities. The rapid response in these measures of HRQoL and physical function parallels the previously reported improvements in the clinical measures (PASI and ACR scores) in patients treated with infliximab.[19] Possibly, improvements in the patient reported outcome measures of HRQoL and physical function can be seen earlier than clinical measures, and may be predictive of clinical improvement. Further examination is needed to determine if early changes in quality of life can reliably predict changes in more objective clinical measures that may require a longer observation period.

This is one of the first studies to show significant improvement in the physical as well as the mental components of the SF-36 in response to treatment in patients with PsA. These two summary scores are constructed so that they are not correlated with each other. Given this, the significant improvements seen in both the physical and the mental summary scores in this trial are impressive and are not often seen with treatment interventions. Overall, patients achieving improvements in both the skin and joint components achieved the greatest HRQoL improvement in both the physical and the mental components of the SF-36. As far as we know, this relative contribution of improvements in the skin and joint components of the disease towards improving patient wellbeing has not been previously reported, and these results highlight the importance of treating psoriasis as well as arthritis in patients with PsA.

The findings of the IMPACT 2 study show that infliximab significantly improved HRQoL and physical function in patients with PsA. We also found that both psoriasis and arthritis responses were important from a patient perspective, with maximal improvement in HRQoL seen in those patients who achieved both a skin and a joint response. Thus, improving both arthritis and psoriasis is important in achieving optimal patient outcomes. We feel it is important to include improvement in HRQoL when making a global assessment of the response to treatment, as this is one of the key measures used to determine clinically meaningful improvement when treating both the arthritis and the psoriasis with a single agent in patients with PsA.

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